Sami Leppämäki

The Effect of Exercise and Light on Mood

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Academic Dissertation

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TIIVISTELMÄ

Säännöllinen liikunta vaikuttaa väestötutkimusten perusteella olevan yhteydessä parempaan mielialaan. Masennuspotilailla liikuntahoidolla on saatu myönteisiä tuloksia. Kirkasvalo on tehokas hoito talvimasennuspotilailla, ja helpottaa myös lievempää, säännöllisesti talvisin toistuvaa kaamosoireilua.

Tätä tutkimusta varten kerättiin vapaaehtoisia työterveyshuoltojen kautta, ja 244 tutkittavaa arvottiin osallistumaan joko liikuntaryhmiin, kirkasvalossa tai normaalissa valaistuksessa, tai rentoutus-venytysryhmiin, joko kirkasvalossa tai normaalissa valaistuksessa. Tutkimus kesti kahdeksan viikkoa ja tutkimusjakso oli sijoitettu keskelle talvea. Tutkittavat arvioivat mielialaansa tutkimuksen aikana käyttäen Hamiltonin masennusasteikon itsetäytettävää versiota. Tutkimuksen keskeinen löydös oli, että sekä liikunta että kirkasvalo paransivat tutkittavien mielialaa ja vähensivät masennusoireita. Kirkasvalo oli liikuntaa tehokkaampi ns. epätyypillisten masennusoireiden hoitamisessa. Epätyypillisiä masennusoireita ovat ruokahalun kasvu, erityisesti "hiilihydraattinälkä", painon nousu ja unen tarpeen ja määrän kasvu. Näitä oireita on useammin talvimasennuksesta kärsivillä kuin ihmisillä, joiden masennus ei ole vuodenaikariippuvaista.

Fyysinen harjoittelu vähintään kaksi kertaa viikossa on tehokas masennusoireiden lievittäjä pimeimpänä vuodenaikana. Kirkasvalohoidolla on liikuntaa enemmän vaikutusta epätyypillisiin masennusoireisiin, jotka usein liittyvät talvisin toistuvaan vuodenaikaoireiluun.

Avainsanat: kaamosmasennus, masennus, kuntoliikunta, valohoito

Sami Leppämäki, The effect of exercise and light on mood

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SUMMARY

In the study "The effect of exercise and light on mood" 244 working-age volunteers were recruited and randomized in treatment groups with exercise either in bright light or normal illumination, or relaxation / stretching either in bright light or normal illumination. The subjects rated their mood using the Hamilton Depression Rating Scale at the start and finish of the 8-week study period. Exercise sessions were 2-3 times per week and relaxation / stretching sessions 1-2 times per week.

It was found that physical exercise was an effective treatment of depressive symptoms (minor depression, sub-syndromal depression), and BL was effective in the treatment of so-called atypical depressive symptoms, which include increased appetite, weight-gain, and hypersomnia. Exercise and BL were found to be safe and effective interventions, which may relieve depressive symptoms during wintertime, and may act as preventive measures against the emergence of depression.

Keywords: seasonal affective disorder, depressive disorder, exercise therapy, phototherapy, intervention studies

1. LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original publications, which are referred to in the text by Roman numerals I-IV. In addition, some unpublished data are presented.

I Partonen T, **Leppämäki S**, Hurme J, Lönnqvist J. Randomized trial of physical exercise alone or combined with bright light on mood and health-related quality of life.

Psychological Medicine 1998; 28: 1359-64.

II **Leppämäki S**, Partonen T, Lönnqvist J. Bright-light exposure combined with physical exercise elevates mood

Journal of Affective Disorders 2002; 72: 139-44.

III **Leppämäki S**, Partonen T, Hurme J, Haukka J, Lönnqvist J. Randomized trial of the efficacy of bright-light exposure and aerobic exercise on depressive symptoms and serum lipids.

Journal of Clinical Psychiatry 2002; 63: 316-21.

IV **Leppämäki S**, Haukka J, Lönnqvist J, Partonen T. Drop-out and mood improvement: a randomised controlled trial with light exposure and physical exercise [ISRCTN36478292].

BMC Psychiatry 2004; 4: 22.

2. ABBREVIATIONS

ATYP	Atypical depression symptom score
BDI	Beck Depression Inventory
BNSQ	Basic Nordic Sleep Questionnaire
BL	Bright Light
BLT	Bright Light Treatment
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; American Psychiatric Association, 1994, revised 2000
GSS	Global Seasonality Score
HDRS	Hamilton Depression Rating Scale
MAO	Monoamine-oxidase
MDD	Major Depressive Disorder
POMS	Profile of Mood States
RHT	Retinohypothalamic Tract
SAD	Seasonal Affective Disorder
SCN	Supra-chiasmatic Nucleus
SIGH-SAD-SR	Structured Interview Guide for the Hamilton Depression Rating Scale – Seasonal Affective Disorders Version Self-Rating Format
SPAQ	Seasonal Pattern Assessment Questionnaire
SSRI	Selective Serotonin Re-uptake Inhibitor
sub-SAD	Subsyndromal Seasonal Affective Disorder

3. ABSTRACT

The aim of the study was to compare the effect physical exercise and bright light has on mood in healthy, working-age subjects with varying degrees of depressive symptoms. Previous research suggests that exercise may have beneficial effects on mood at least in subjects with depression. Bright light exposure is an effective treatment of winter depression, and possibly of non-seasonal depression as well. Limited data exist on the effect of exercise and bright light on mood in non-clinical populations, and no research has been done on the combination of these interventions.

Methods

Working-age subjects were recruited through occupational health centres and 244 subjects were randomized into intervention groups: exercise, either in bright light or normal lighting, and relaxation / stretching sessions, either in bright light or normal gym lighting. During the eight-week intervention in midwinter, subjects rated their mood using a self-rating version of the Hamilton Depression Scale with additional questions for atypical depressive symptoms.

Results

The main finding of the study was that both exercise and bright-light exposure were effective in treating depressive symptoms. When the interventions were combined, the relative reduction in the Hamilton Depression Scale was 40 to 66%, and in atypical depressive symptoms even higher, 45 to 85%. Bright light exposure was more effective than exercise in treating atypical depressive symptoms. No single factor could be found that would predict a good response to these interventions.

Conclusions

Aerobic physical exercise twice a week during wintertime was effective in treating depressive symptoms. Adding bright light exposure to exercise increased the benefit, especially by reducing atypical depressive symptoms. Since this is so, this treatment could prevent subsequent major depressive episodes among the population generally.

4. INTRODUCTION

4.1 Depressive disorders - public health problem of the new millennium

Depression places an immense burden on Western society. It is a common disease, the one-year point prevalence of depression in Europe being estimated at at least 5% of the population [1], with greater prevalence among women. Lifetime prevalence is considerably higher, estimates ranging from 10 to 30%. Depression ranked as the fourth leading cause of burden among all diseases [2], and causes significant suffering for the individual, increasing the use of health services. Most depressed people are however not treated at all [3], or are receiving inadequate treatment. Depression significantly impairs not only mental well being, but also other factors collectively referred to as health-related quality of life [4].

Depressive disorders can best be conceptualised as a continuum ranging from transient feelings of sadness to major depressive disorder (MDD). MDD can be further divided according to the severity and number of symptoms and, in the severest forms of depression, psychotic symptoms or extreme psychomotor retardation may be present. The categorical diagnostic system currently used has major disadvantages, the most significant of which is that it really does not represent the true spectrum of depressive disorders. A more flexible, dimensional model is called for to broaden the diagnostic boundaries [5,6]. Research criteria for minor depression appear in appendix B of DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; American Psychiatric Association, 1994, last revision 2000), which require the presence of 2 to 4 symptoms of MDD.

Minor depression, sub-syndromal depression, and depressive symptoms refer to the same core phenomenon [7]. Research on minor depression suffers somewhat from the heterogeneous definition of minor depression, but some findings seem to be relatively robust. First, minor depression considerably increases the risk of developing major depression. Relative risk ratio has varied from 1.15 to 9.73 in general population studies [8]. This also holds for patients with minor depression, who have never suffered from major depression [8]. This is an important distinction, because the residual phase or partial remission of major depression also increases the risk of developing a new major depressive episode. Minor depression can thus be considered both a precedent and antecedent of major depression, though most patients with minor depression never develop a major depressive episode.

Second, although not classified as having major depression, people with depressive symptoms still experience major problems related to their mental health. Subjects with depressive symptoms reported significantly higher levels of household strain and social irritability as well as limitations in physical or job functioning compared to subjects with no symptoms [9]. Minor depression is associated with significantly higher use of health services and more impairment when compared to asymptomatic controls [10]. The quality of impairment caused by minor, or subsyndromal, depression is thus comparable to major depression.

4.2 What can be done? Treatment options

Depressive symptoms and minor depression seem to pose a major public health problem which is as yet largely unrecognised and underestimated. Should these subjects be treated? Treatment of major depression has been well documented. Antidepressants and psychotherapy (cognitive-behavioural or interpersonal) alone or in combination can currently be considered the standard treatment. Studies on the treatment of minor depression are few. Eight weeks of cognitive-behavioural therapy seemed effective in reducing depressive symptoms [11], whereas telephone-based problem-solving therapy did not differ from treatment-as-usual or stress management treatment in a study which suffered from a high drop-out rate [12]. Although all treatments offered seemed to reduce depression scores, the authors conclude that watchful waiting may be a reasonable management alternative. NICE guidelines come to the same conclusion (National Institute for Clinical Excellence (2004) Clinical Guidelines for Management of Depression in Primary and Secondary Care, http://www.nice.org.uk/CG023NICEguideline), also stating that antidepressants are not recommended for the initial treatment of mild depression because of a poor risk-benefit ratio. However, according to a recent study, there is a low likelihood of spontaneous remission (9-13%) for treatment-seeking subjects with minor depression in primary care [13].

Antidepressant treatment of minor depression or related conditions has been poorly studied. Original trials with tricyclics gave mixed results [14], newer antidepressants seeming to be more promising. Fluoxetine reduced significantly depressive symptomatology in a double-blind, 12-week study [15]. Fluvoxamine decreased substantially depressive symptoms and improved psychosocial functioning in an open-label, 8-week study [16]. Studies are all short, eight to twelve weeks, and no studies concerning the long-term efficacy or safety of these drugs in this population have been published.

Obviously, there is a need for interventions targeting the depressive symptomatology of these subjects. Effective strategies to prevent depression are also called for [17]. At least two promising interventions, physical exercise and bright light, have been tested for the treatment of major depression. Exercise therapy has been found to possibly be as effective as an antidepressant, sertraline, in relieving symptoms of depression in patients with diagnosed major depression [18]. In older subjects suffering from depression

or a large number of depressive symptoms physical exercise may be efficient in reducing clinical depression and depressive symptoms at least in the short-term [19]. Bright light exposure is the treatment of choice in recurrent seasonal depression, especially the winter type, in which depressive episodes begin in the late autumn / early winter, and remission follows in the spring. In a recent Cochrane review, light therapy was found to have modest efficacy in non-seasonal depression as well [20]. Lower daily light exposure was associated with increased atypical depressive symptoms in middle-aged subjects in the San Diego area [21]. The authors conclude that many Americans may be receiving insufficient light exposure to maintain optimal mood.

These two interventions, exercise and light, seem also to be efficacious in subsyndromal, or sub-threshold depressive states, as well as being safe, relatively well-tolerated and cheap. They also have the potential to be adopted by a large portion of the population as a part of a healthier lifestyle, and in the end exercise and light could be important factors contributing positively to public health. However, there are several factors of interest: 1) what is the interaction between exercise and light? Is the combined effect on mood positive, negative, or neutral? 2) Is seasonality a factor? Light therapy is known to be most effective on seasonal depression, but no studies exist on the effect of exercise on seasonal depressive disorders.

5. REVIEW OF THE LITERATURE

5.1 Seasonal mood swings

5.1.1 The rhythms of life

Man has always been intrigued by the cyclical nature of the environment. The surrounding world seems to have an intrinsic rhythm, reflected in the sun rising and setting, tidal ebb and flow, phases of the moon, and the seasons. To survive in such an environment, organisms must somehow adapt to these sometimes abrupt, but often slower rhythms affecting the amount of sunlight and temperature. Beginning from the 19th century, understanding of how living organisms achieve this has slowly increased. Rather than being passive spectators of the external rhythms, every living creature has its own internal rhythm, ticking away regardless of the external time. These circadian (Latin circa=approximately, dies=a day) rhythms exist in one-celled organisms as well as humans, where the main clock has been located in the cells of the supra-chiasmatic nucleus (SCN). Research on biological clocks has exploded in recent years as more and more somatic diseases, for example, some types of breast cancer, have been linked to disturbances in the delicate balance of the internal clock [22].

Although the circadian rhythms are generated at molecular level, they must, of course, interact with the environment to be useful to the organism. Light has been shown to be the strongest external *Zeitgeber* (German for time-giver) needed to synchronise the internal clock to match the environment. Light is transduced into a neural signal in the retina and conveyed to the SCN core along the retinohypothalamic tract (RHT). Other *Zeitgebers* exist, such as ambient temperature, physical exercise, and social rhythms, but they are usually masked by the effect of sunlight. In man, the circadian rhythm, which body core temperature and melatonin secretion follows, is slightly longer than 24 hours (about 24 hours 11 minutes [23]). Thus a subject placed in conditions in which all external environmental cues are eliminated, follows his internal rhythms, now "free-running", and the daily activity rhythm and internal, physiological rhythms slowly advance in clock-time. The ability of the circadian clock to be reset by an external *Zeitgeber* allows it to maintain a temporal alignment with local time.

5.1.2 Seasonal affective disorder

5.1.2.1 History

Seasonal changes have probably affected mood through the centuries, as Magnússon indicates [24]. However, it was not until 1984 that Norman Rosenthal's group from the National Institute of Mental Health (NIMH) in Bethesda published their preliminary findings with bright light therapy, describing a new syndrome called Seasonal Affective Disorder (SAD) [25]. The story of SAD and light therapy is a fascinating one, and centres on one man, Herbert E. Kern, who was a research scientist who suffered from bipolar disorder. He had recorded his mood swings from late the 1960s, noting that his mood changes were clearly seasonal and related to sunlight intensity and day length. He patiently sought an answer to his problems, and ultimately contacted the Dr Alfred Lewy at the NIMH [26]. Kern became the first patient to be treated with bright light therapy [27, 28].

However, in 1946, Dr Hellmut Marx, a German endocrinologist, described a patient with recurrent winter depression treated with sunlamps [29]. Quoted by Wehr and Rosenthal in their letter replying to Kern and Lewy [26]: "The darkness of the polar winter gave him a lot of trouble...He complained of a general loss of efficiency, felt stale, fatigued, listless, and...depressed for no reason. His appetite...at times increased to the point of bulimia...In the spring of 1943 he rapidly recovered with the return of sunlight." An accurate description of the symptoms of SAD.

5.1.2.2 Diagnosis

The original criteria for SAD [25] require depression to develop during the autumn or winter with remission following in the spring or summer, which describes the winter-depression type of SAD. A summer SAD has also been described [30], but seems to be a rarer condition, and may possibly be an entirely different disorder, as to etiology and treatment. In this presentation SAD will imply winter SAD, unless otherwise specifically stated.

The professional community soon accepted SAD as a concept , and the original criteria were transformed into diagnostic criteria as early as 1987 (Diagnostic and Statistical Manual of Mental Disorders, Third revised version, [DSM-III-R], American Psychiatric Association 1987). DSM-IV (American Psychiatric Association 1994) currently recognises SAD as a specifier of bipolar or major depressive disorder, denoting a seasonal pattern in major depressive episodes. Table 1 lists the DSM-IV criteria. It is noteworthy that the main criterion for SAD is the appearance of depressive episodes at approximately the same time of every year (or at least two years in a row). This does not convey anything about the clinical picture of SAD. Do major depressive episodes somehow differ in patients with and without a seasonal pattern?

Table 1. DSM-IV criteria for the seasonal pattern of major depressive episodes

A regular temporal relationship between the onset of major depressive episodes in bipolar I or bipolar II disorder or major depressive disorder, recurrence, and a particular time of the year (for example, regular appearance of the major depressive episode in the autumn or winter). **Note:** do not include cases in which there is an obvious effect from seasonal-related psychosocial stressors (for example, regularly being unemployed every winter)
Full remissions (or a change from depression to mania or hypomania) also occur at a characteristic time of year (for example, depression disappears in the spring).
In the last two years, 2 major depressive episodes have occurred that demonstrate the temporal seasonal relationships defined in the two criteria above, and no non-seasonal major depressive episodes have occurred during the same period.
Seasonal major depressive episodes (as described above) substantially outnumber the non-seasonal major depressive episodes that may have occurred over the individual's lifetime

The DSM-IV includes an "atypical features" episode specifier for a major depressive episode. For the episode to be defined as "atypical", the patient's mood must be reactive (i.e., it brightens, even for a short while, in response to positive events, in contrast to "melancholic" mood). In addition to mood reactivity, at least two of the following symptoms must be present: weight gain or increase in appetite, hypersomnia, leaden paralysis (i.e., a heavy, leaden feelings in the limbs), and a long-standing pattern of interpersonal rejection sensitivity. Studies of SAD have, from the very beginning described patients commonly exhibiting an increase in appetite, especially carbohydrate craving, weight gain and hypersomnia, symptoms collectively called "reverse vegetative symptoms" [25]. Is SAD a variant of atypical depression?

A Canadian group compared atypical symptoms in SAD patients with non-seasonal MDD patients [31]. SAD patients had higher scores only in hypersomnia and hyperphagia. The groups did not differ in mood reactivity, and rejection sensitivity was greater in the non-seasonal group. Since only 26% of the study patients with SAD met the DSM-IV criteria for atypical depression, the authors concluded that the overlap between atypical depression and SAD is in the reverse vegetative symptoms only. Comparison of clinical characteristics in Swedish patients with seasonal and non-seasonal depression found that

patients with seasonal pattern reported more increased appetite and carbohydrate craving, and non-seasonal patients had significantly higher scores on the Hamilton Depression Rating Scale [32]. The authors conclude that clinical symptomatology has low specificity in differentiating seasonal and non-seasonal depression [32]. Table 2 shows the frequencies of some symptoms in SAD. These are comparable to non-seasonal major depression, and do not distinguish the two disorders.

It seems that the only clinical feature separating SAD and MDD is the SAD patients' rapid and robust response to bright light therapy. The patient's history is important in that many relate that their symptoms vanished when they spent their winter vacation in a place considerably closer to the equator, and patients' moods may react to very slight changes in ambient lighting.

Table 2. Symptoms and signs in patients with winter SAD (reprinted with permission from [71])

Frequent	%
Sadness	96
Decreased activity	96
Social misfortune	92
Anxiety	86
Irritability	86
Occupational misfortune	84
Daytime tiredness	81

Fairly frequent	%
Increased sleep	76
Poor quality of sleep	75
Increased weight	74
Carbohydrate craving	70
Decreased libido	68
Increased appetite	65

Fairly infrequent	%
Suicidal thoughts	35
Decreased sleep	31

Infrequent	%
Mixed or no change in appetite	17
Mixed or no change in weight	17
Decreased appetite	15
Decreased weight	7
Mixed or no change in sleep	5
No change in activity	2

5.1.2.3 Seasonal Pattern Assessment Questionnaire

The SPAQ (Seasonal Pattern Assessment Questionnaire) [33] is practically the only instrument used to diagnose SAD in population surveys. It was originally created to measure seasonal changes in mood and behaviour, but was soon adopted as a screening / diagnostic instrument for SAD [34]. The essential feature of SPAQ is the Global Seasonality Score (GSS, also referred to as SSI, Seasonality Score Index), which consists of six items: mood, weight, appetite, vitality, social activity, and length of sleep. Since the subject is asked to estimate how much he/she feels these change with seasons, and rate each item on a scale from 0 (no change) to 4 (extremely marked change), the GSS may yield values from 0 to 24. A second criterion for SAD is whether the subject considers these seasonal changes a problem and, if yes, to what degree. The possible answers and corresponding values are: 1=a mild problem, 2=a moderate problem, 3=a marked problem, 4=a severe problem, 5=a disabling problem. For a diagnosis of SAD, the subject must score at least 10 points on the GSS and experience the change as at least a moderate problem.

Along with these criteria, the concept of subsyndromal SAD (sub-SAD) was introduced [35] to identify those subjects with clear-cut seasonal complaints that however are not severe enough for a diagnosis of SAD (For the original research criteria for sub-SAD, see Table 3). There has been some confusion over the original SPAQ criteria, and varying criteria have been used in prevalence studies [24]. The original SPAQ-criteria for sub-SAD require a GSS of at least 8 and the answer to the question "having a problem with seasonal changes" is either a problem or not. If GSS is 10 or higher, seasonal changes must be no more than a mild problem [34]. For lower scores (8-9), the criterion was soon rephrased to "experience seasonal change as at least a mild problem" [36], which is now the most commonly used cut-off for sub-SAD.

The psychometric properties of the SPAQ have been studied extensively. Magnússon et al. (1997) found that the 6 items of the GSS correlated well in a population study in Iceland (n=587), and that the scale had high internal consistency (Cronbach’s alpha=.82) [37]. They concluded that GSS is well constructed and reliable in measuring seasonal changes. In a study of college students (n=148), Young et al. (2003) replicated the findings of Magnússon et al. [38], finding good internal consistency (Cronbach’s alpha=.81) and two-month test-retest reliability (0.76). Their findings support the view that SPAQ is a valid instrument for measuring seasonality. The GSS has relatively good test-retest reliability, at least in the short term, but this decreases with time [39]; obviously so, as treatment, whether by bright light or psychotropic drugs, is bound to influence the course of illness.

Table 3. Research criteria for sub-SAD

1) A history of some difficulty during the winter months that has occurred on a regular basis (at least two consecutive winters) and has lasted for a sustained period of time (at least 4 weeks). Examples of these difficulties are decreased energy, decreased efficiency at work (e.g., concentration, completing tasks), decreased creativity or interest in socializing, and change in eating habits (e.g. eating more carbohydrates), weight (gaining weight), or sleep patterns (more sleep).
2) Subjects regard themselves as normal, i.e., not suffering from an illness or disorder.
3) Subjects have not sought medical or psychological help specifically for these difficulties, nor has anyone else suggested that they should do so.
4) People who know them well do not recognize that they have a problem, or if they do, attribute it to circumstances such as "flu" or "overwork".
5) The symptoms subjects experience do not disrupt their functioning to a major degree, e.g., calling in sick several times per winter, or severe marital discord.
6) No history of major affective disorder in the winter.
7) No serious medical illness.

SPAQ is a good measure of seasonality and a screening tool to identify possible cases of seasonal mood disorders. It has also been widely used as a diagnostic instrument. Magnússon (1996) found excellent sensitivity and specificity (94% and 73% respectively) for a "winter problem" group, which included both SAD and sub-SAD [40]. The SPAQ however had little ability to distinguish between subjects with SAD and sub-SAD. Mersch and colleagues (2004) compared four different groups: SAD patients, non-seasonal depressed outpatients, non-depressed outpatients, and a control group [41]. The SAD criterion of the SPAQ showed good specificity (94%), but a considerably lower sensitivity (44%).

Mersch et al. [41] raise two concerns based on their results. First, they complain about low sensitivity. They admit however that most of the SAD patients in their study had attended their out-patient clinic for years and received bright light therapy every winter. These patients had thus received effective treatment for their symptoms, preventing the worsening of symptoms and occurrence of severe problems. It seems very probable that these patients' views about the seasonal nature of their symptoms had changed during years of successful treatment. The other point Mersch et al. raise is specificity. There were only a small number of false positives, all in the group of depressive patients (16.7%). The questionnaires in this study were completed in the summer. Many depressed patients complain about seasonal changes, and feel that they fare even worse during the winter. They may be classified as SAD patients on the SPAQ even though they have also non-seasonal depressive episodes or feel more or less depressed all the time. The authors suggest that the studies should be performed during the summer months, and the SPAQ should be accompanied by a validated depression scale to prevent overestimated prevalence figures in the future [41].

The widespread use of the SPAQ as a diagnostic instrument has been criticised. It seems however that the SPAQ has a relatively good internal consistency, and that the items really do catch the essence of "seasonality". As pointed out by Young and colleagues, the question of how accurately the SPAQ identifies cases of SAD may be useful, but it is not one that should or could be used to assess the validity of SPAQ [38]. It seems that the SPAQ works best as a measure of seasonality, both in the population and the individual. This is contrary to what Greg Murray (2003) concluded from the results of his follow-up of 304 subjects: "SPAQ can function as a measure of seasonality of mood in the normal population, but estimates of the extent of individual seasonality should be avoided" [42]. Here seasonality is represented by seasonality of mood, which is only one of the six scales in the GSS. As already mentioned, change in mood is probably not the basic symptom of seasonality. The atypical vegetative symptoms are closer to the "core", and all six scales probably add something essential to seasonality.

5.1.2.4 Epidemiology

Kasper and colleagues (1989) interviewed 416 randomly chosen subjects by telephone in Montgomery County, Maryland (39°N) using the SPAQ [34]. They found a prevalence of 4.3% for SAD and 13.5% for sub-SAD, with a ratio of women to men- of 3.5:1 for SAD and 1.2:1 for sub-SAD. The mean GSS for the whole group was 5.43, with higher scores among younger women. In a more recent study also from the Washington D.C. area, the prevalence of SAD was 5.4% and sub-SAD 9.5% [43]. Since the study population consisted of African American college students, it was not representative of the general population.

In Iceland, the prevalence of both SAD and sub-SAD was found to be significantly lower than in the US (Montgomery County, Nashua, and New York): Age-adjusted prevalence rates for SAD were 3.6% in Iceland (63°N to 67°N) and 7.3% in the USA (39°N to 42.5°N), and for sub-SAD 6.9% and 10.9% respectively [44]. The authors assume this might be because those genetically predisposed towards stronger seasonal variation could have been at a disadvantage in the harsh Icelandic conditions over the centuries. Magnússon obtained interesting results by expanding his study to a group of adults in Canada (Interlake district, Manitoba; 50.5°N) wholly descended from early 19th century Icelandic immigrants [45]. The prevalence rate of SAD was 1.2% and sub-SAD 3.3%, which were again significantly lower than prevalence rates obtained by similar methods in the USA. The combined prevalence rate of SAD and sub-SAD was significantly lower among the immigrant group than among those Icelanders who had stayed faithful to their country. These results seem to support the view that, latitude does indeed influence the expression of seasonality within genetically similar populations.

Telephone interviews with 2015 subjects in Finland yielded prevalence rates for SAD of 3.4% and 21.8% for sub-SAD [46]. A comparative study in Finland and Sweden using mailed questionnaires found prevalence rates for SAD and sub-SAD of 7.1% and 11.8% in Finland and 3.9% and 13.9% in Sweden [47]. Another study in Finland with a representative sample of 1710 subjects from two locations in north and south-west of Finland found a prevalence of 9.5% for SAD and 18.4% for sub-SAD. There was no difference in the prevalence between the two locations studied [48]. Partonen et al. (1993) used a different approach, mailing a depression scale (modified to include atypical symptoms as well) to 1000 employees of the Finnish National Bank during winter, and received 486 questionnaires back [49]. The subjects lived between 60°N and 70°N, but latitude was not found to be influential. Depressed subjects (n=54) were evaluated the following May, and 4 SAD cases were found, which was about 0.8% of those who returned the questionnaire, and 7.4% of the depressed subjects.

Wirz-Justice and colleagues (2003) report a telephone survey using SPAQ in Switzerland (47°N) [50]. Prevalence rates were 2.2% for SAD and 8.9% for sub-SAD. Women comprised 61% of "seasonals" ; no data on the influence of age were reported. The authors included annual hours of sunshine as a variable, but this did not influence prevalence rates of seasonal mood syndromes. They also asked for the subjects' opinions on their indoor lighting conditions and time spent outdoors. Only the former differed significantly, seasonals deeming their lighting conditions worse than non-seasonals.

A Japanese translation of the SPAQ was used to assess seasonality among two age groups: high-school students (n=3237) and adult workers (n=4858) [51]. Subjects were also divided according to the region they lived in, whether the north or south of Japan. Prevalence rates in students were 0.91% for SAD and 2.21% for sub-SAD, and among workers 0.45% and 1.16% respectively. In this study, the summer type of SAD was as prevalent as winter SAD. The sex ratio was equal in both age groups. As seen from these figures, the prevalence of seasonal problems seems to decrease with age. There was no latitude effect among students, but, both SAD and sub-SAD were significantly more prevalent among workers living in northern Japan (0.81% vs. 0.12% for SAD and 1.71% vs. 0.66% for sub-SAD). The authors attribute the lack of latitude effect among students to both geophysical and socio-cultural factors, but also question the reliability of SPAQ in this group.

Murase et al. (1995) followed the mood of Japanese immigrants in Stockholm monthly for a year [52]. The authors hypothesized that seasonal mood swings might be a representation of the peculiar lifestyle and culture of Scandinavian people. However, since people of Japanese origin were found to have lower mood during the winter immediately after they had immigrated to the north, the authors admit that chronobiological factors might also be influential. Surprisingly however, immigrants who had resided more than ten years in Stockholm had more seasonal mood variation than those who had immigrated less than two years before. The more time you spend in Scandinavia, the gloomier you become?

What about people living in more temperate climates? In a psychiatric teaching centre in Cagliari, Italy, all patients treated for a mood disorder (n=1507) were retrospectively assessed for the presence of a seasonal pattern according to DSM-III-R criteria [53]. Seasonal mood disorder was diagnosed in 146 patients, 9.7% of all patients with a mood disorder. Of the subjects with seasonal pattern, 71% were women. Recurrent major depression was slightly more common (51%) than bipolar disorder (49%) amongst those with seasonal mood disorder. In this clinical population, authors found that the two patterns of seasonality (fall-winter depression with or without spring-summer mania or hypomania, or spring-summer depression with or without fall-winter mania or hypomania) to be equally frequent. Thus, if the prevalence of mood disorders is approximately 8 to 10% in the general population, and 5% of patients with any mood disorder have the winter seasonality pattern, the prevalence of SAD would be 0.4 to 0.5% [53].

Nearer to the equator, in the Philippines (Quezon City, 14°N), the prevalence rates for both SAD and sub-SAD were 0% [54]. Down under, in the southern hemisphere, prevalence rates have also tended to be lower than in the Europe or USA. Parslow and colleagues report the results of a community-based study of 7485 individuals in Canberra (35°S) [55]. Of the participants, 5.3% met the SPAQ criteria for season-dependent affective disorder, but the figure was for all seasons totalled. Of those who reported experiencing a worst month, 59.3% identified a winter month, so that a rough estimate for the prevalence rate of SAD is approximately 3%.

5.1.2.5 Treatment

Exposure to bright artificial light is considered the first-line treatment of SAD. As bright light therapy (BLT, light treatment, phototherapy) will be reviewed in Chapter 5.2, other available treatment methods for SAD will be discussed in this section.

5.1.2.5.1 Drug treatment

Although light therapy is efficacious, there is still a significant minority of non-responders to light exposure. Since some patients may decline light treatment as too time-consuming, and some experience side-effects such as irritation of the eyes, headache or agitation, there seems to be a need for additional treatments. Half of SAD patients treated with BLT were also receiving psychopharmacological treatment [56]. Drug treatments for SAD have been studied relatively little. An additional problem is that most of the studies have been done on antidepressants, and follow guidelines for the treatment of depression. There is no evidence-based information on how we should treat those SAD patients with a bipolar course of illness [57], as they have been excluded from these drug trials.

To date, no psychoactive agent has been licensed specifically for the treatment of SAD. Agomelatine (S 20098) is a melatonin agonist and selective antagonist of 5-HT2C receptors, and as such has a unique pharmacological profile. It has been shown to be efficacious in the treatment of major depressive disorder [58], and is currently in the clinical trial phase for SAD patients. Exogenous melatonin administration, however, whether given in the early morning or late at night, has not been effective in the treatment of SAD [59].

Because of the often-present atypical symptoms and anenergy in SAD, hopes were placed on antidepressants with adrenergic properties, such as moclobemide, a reversible inhibitor of monoamine-oxidase (MAO). Moclobemide was compared to placebo in a double-blind study in Norway [60]. The double-blind phase lasted only for three weeks, and no significant

difference in response or remission was found. The authors note, however, that atypical symptoms reduced significantly more in the moclobemide group after the first week. Moreover, moclobemide and fluoxetine, a selective serotonin reuptake inhibitor (SSRI), were found equally effective in the treatment SAD [61]. Neither did the response rate did differ according to whether patients had SAD or depression without a seasonal cycle.

Other drugs which have been studied for the treatment of SAD include the norepinephrine and dopamine re-uptake inhibitor bupropion [62], selective norepinephrine re-uptake inhibitor, reboxetine [63], and an irreversible inhibitor of MAO, tranylcypramine [64].

Modern, double-blind, placebo-controlled studies, with sufficient sample sizes on SAD are rare. Two SSRI's, sertraline [65], and fluoxetine [66], have been found to be effective and well-tolerated drugs in the treatment of SAD, when clinical response was defined as the endpoint.

5.1.2.5.2 Other treatments

Perhaps because SAD seems to have strong biological underpinnings, other treatment options have not been studied extensively. A preliminary report shows that cognitive-behavioural therapy holds promise as a treatment option for SAD [67]. Sleep deprivation, effective in non-seasonal depression, could be useful in selected patients with SAD [68]. Chronobiological treatments for other affective disorders should also be studied in SAD patients [69]. Exercise has not been researched specifically as treatment of seasonal affective symptoms. In a study of "natural" light treatment of SAD, the patients were treated with a daily 1-h morning walk outdoors, but the study did not separate the effects of exercise and light [70].

5.2 Bright light therapy

5.2.1 History

The history of bright light therapy is closely related to SAD. The first report on SAD, also discussed preliminary findings with light therapy [25]. This may have moulded thinking about SAD for years, which is not entirely positive. Viewing SAD simply as a "lack-of-light-syndrome" may have obscured its complexity.

5.2.2 Technical details and side effects

At least two properties of light, intensity and spectrum, have been investigated to determine the optimal treatment regimen. Studies of bright white light-induced melatonin suppression in humans led to studies on the treatment of SAD with bright light [27, 72]. Broad-spectrum white fluorescent light and cool white fluorescent light have been found to be equally effective [73]. Broad-spectrum white light was as effective without ultraviolet emission as with UV rays, which has led to elimination of UV from light treatment devices [74]. A meta-analysis of the spectral properties of phototherapy suggested that light of short to medium wavelengths (blue/green/yellow) was essential for the therapeutic effect, while red wavelengths were relatively ineffective.

Standard light treatment has generally been administered through light boxes, with or without diffusing screens. A dose-effect relationship has been established, and effective doses of BLT seem to depend on the intensity of the light. With intensities of at least 10,000 lx, 30 minutes in the morning suffices. The minimum intensity considered to be "bright light" has been approximately 2500 lx, and the treatment should then last for at least 2 hours in the morning. Illumination outdoors varies with weather and season, from below 2000 lx on a rainy day to 10,000-100,000 lx in direct sunshine. There is typically 100 lx or less at home, and about 300-500 lx in the office environment.

BLT is generally extremely well tolerated. Concerns about ocular safety seem not to be warranted. Even so, long-term wintertime use (3 to 6 years) did not cause any ocular changes [75]. Still, patients with pre-existing ocular abnormalities or using photosensitizing drugs should use BLT only with regular ophthalmological examinations.

Common side effects include eye-strain, irritation and headache, but these seldom lead to treatment cessation. However, if BLT is administered in the evening, insomnia is common [76]. Suicidal tendencies [77] and even suicide [78] have been reported as possible complications of BLT.

5.2.3 Bright light therapy and mood

Clinical studies on BLT generally suffer from lack of a credible placebo. A common placebo condition is dim red light, which might not suffice. It is not possible to "blind" patients to whether they receive BLT or dim light. However, innovative placebo conditions, such as sham negative-ion generators have been used [79], and BLT has been extensively studied both in the treatment of SAD and non-seasonal affective disorders.

5.2.3.1 Efficacy in seasonal mood disorders

The most recent review and meta-analysis of BLT in the treatment of SAD confirmed the earlier findings that BLT is efficacious, with effect sizes equivalent to those in most antidepressant trials [80]. The authors point out problems with study design, only 8 studies altogether meeting their inclusion criteria. The effect size was high, .84 (95% CI .60 to 1.08), compared to the placebo condition.

Studies of BLT generally show improvements in 50-80% of patients with SAD. Atypical depressive symptoms are the best predictors of a good response to BLT [81]. The effect on depressive symptoms usually appear after one to two weeks of daily BLT sessions. Since the effect does not last for longer periods, the treatment must continue after remission as maintenance treatment, until "natural" remission. A daily treatment regimen is most frequent in studies of BLT. No studies exist of "low-dose" BLT, with treatment given only 2 or 3 times per week. Some preliminary evidence suggests that repeated bright-light exposure could alleviate distress and lift mood even in the absence of SAD or sub-SAD [82].

5.2.3.2 Efficacy in non-seasonal mood disorders

A recent Cochrane review investigated the efficacy of BLT for non-seasonal depression [20]. The authors included 49 reports based on twenty studies in their systematic review. Response to bright light was significantly better than to control treatment in studies of high quality, in those studies where BLT was administered in the morning, and when patients were sleep deprivation responders. The authors conclude that BLT seems to offer modest though promising anti-depressive efficacy for patients suffering from non-seasonal depression. For the best results, BLT should be given in the morning. The effect was most apparent during first week of the treatment. The authors also note that hypomania was more frequent among the bright light group than the control treatment group.

Golden et al. (2005) included 3 studies [83-85] comparing BLT to placebo (dim red light) in non-seasonal depression in their review and meta-analysis [80]. The effect size was .53 (95% CI .18 to .89) and highly significant ($p<.003$). In the same review and meta-analysis, BLT was not found to be effective as a supplementary treatment in non-seasonal depression [80].

5.3 Physical exercise and mood

5.3.1 Population studies

Low levels of physical activity have been linked to an increased risk of depression in population studies [86-90]. In the Harvard alumni study, Paffenbarger observed >10,000 alumni aged 23 to 27 years. The endpoint was the outbreak of clinical depression. Rates of depression were lower among the physically active and sports players [86]. Hassmén et al. (2000) found that those exercising 2 to 3 times a week in the Finnish population had the lowest BDI scores [89]. However, they also report that those exercising on a more regular basis had somewhat higher BDI scores.

A greater prevalence of depression and no regular physical exercise were also significantly associated in an epidemiological interview study of 1244 older people (65 to 84 years) [91]. An eight-year follow-up of the study participants showed that a decrease in the intensity of physical exercise seemed to increase the risk of depressive symptoms [92]. Community-dwelling adults (n=1947) from the Alameda County study were followed-up for five years [93]. Physical activity was measured on an eight-point scale, depressive symptoms using criteria from DSM-IV, and age, sex, ethnicity, financial strain, chronic conditions, disability, body mass index, alcohol consumption, smoking, and social relations were taken into account. Even after these adjustments, physical activity had a protective effect for both prevalent and incident depression.

In the Upper Bavarian Field Study of 1536 people, the odds ratio for depression was significantly higher for the physically inactive than the regular exercisers [94]. However, low physical activity at baseline was not a risk factor for developing depression at follow-up of 5 years. In a study of 973 physicians, data were collected on self-reported physical activity in medical school and midlife [95], no correlation between exercising and self-reported depression and psychiatric distress being observed. In a cross-sectional and prospective study of men and women aged 50 years or over, exercisers were found to have less depressed mood, but exercise did not protect those not clinically depressed at baseline against future depressed mood [96].

Epidemiological studies however cannot resolve the question of causality, and the correlational relationship between exercise and depression can also be viewed otherwise. For example, in a 5-year follow-up study of older people, it was concluded that depressed older people are at high risk of physical disability [97]. In an attempt to explain this connection, Sexton et al. found that though mood and exercise were correlated, the only directional relationship they found was that recreational exercise had an inconsistently positive effect on mood in those with sedentary occupations [98].

The link between physical activity and mood is probably very complex, with many obscuring factors, not all of which can be removed from the analysis. However, from an epidemiological point of view, there seems to be enough evidence to say that physical activity and mood are positively correlated, and that higher levels of physical activity can protect one from clinical depression to a certain extent [86-90].

5.3.2 Exercise as a treatment for depressive disorders

Since many studies, especially older ones, from the 1980's or earlier focusing on the effect of physical exercise on depression suffer from methodological limitations, the early optimism seems not fully warranted [99, 100].

In a systematic review and meta-regression analysis of randomised controlled trials of exercise as an intervention in the management of depression, the authors express their concern over the poor quality of most of the research [101]. However, exercise therapy was effective in treating depression, compared with no treatment or as a supplement to standard treatment. Nine studies used the BDI as an outcome measure, and the weighted mean difference in the Beck score was -7.3 (-10.0 to -4.6). Four studies which compared exercise to cognitive psychotherapy found that exercise treatment was as effective as cognitive therapy in the treatment of depression. The previous findings thus seem to hold since exercise treatment is better than no treatment in mild to moderate major depression and is as least as effective as various forms of psychotherapy [102, 103].

Most studies on exercise and depression have used aerobic exercise, but it is probable that similar results can be achieved with non-aerobic forms of exercise. In their review Lawlor&Hopker [101] note that the type of exercise and the variation in results between the studies were not associated. Direct comparisons between anaerobic and aerobic exercise seem to confirm this finding [104-106]. One much quoted study suggests that participation in physical activity rather than cardiovascular fitness was the factor associated with better mood [107], and that high initial exercise intensity may even inhibit formation of new exercise habits, and thus work negatively [106]. Moses et al. compared the effects of two training programmes of differing intensities, finding that the improvements in mood in the moderate-intensity group were greater than in the high-intensity group [108]. An increase in cardiovascular fitness does not seem to be necessary for mood improvement.

Blumenthal et al. compared exercise treatment with and without an antidepressant (sertraline) to sertraline alone on 156 older (≥50 years) patients with major depression [18]. Although patients in the medication groups had a faster initial response after the 16-week trial, all groups exhibited statistically and clinically significant reductions on the Hamilton and Beck depression scores, and there were no differences between the groups. However, this study lacked a 'no treatment' control group.

An optimal ’dose’ for exercise treatment cannot be determined from the present research evidence [109]. This important question is addressed for the first time in a recently published study [110]. The 72 subjects who started the study (1664 were screened) had mild to moderate depression, and were randomized into either an: "Public Health Dose" (17 kcal/kg/week) or "Low dose" (7 kcal/kg/week), or exercise-placebo exercise group, which was stretching in this study. Remission was the defined endpoint, and only the "Public Health Dose" seemed efficacious, "Low Dose" being no more effective than placebo. There were several problems with this study however, one of which was the tremendous drop-out rate (60%) from the control group.

Recruitment seems a major problem in studies with exercise therapy. Mather et al. (2002) screened 1885 patients to get 86 subjects in their trial [111]. Their treatment regimen consisted of supervised, predominantly weight-bearing exercise, twice a week for 10 weeks. The patients were older adults (>53 years) with a poorly responsive depressive disorder – all had had at least one unsuccessful 6-week trial of anti-depressive medication before study entry. Their exercise-placebo condition was health-education talks. At 10 weeks there was a significantly higher proportion of patients in the exercise group who had experienced at least a 30% decline in the HDRS. The effect was not sustained at follow-up (34 weeks).

Since more than half of the participants in exercise studies generally continue with regular exercise after the termination of the training program, the long-term effects of exercise treatment seem promising: [99]. At the six-month follow-up of their trial, Babyak et al. (2000) found that remitted subjects in the exercise group had significantly lower relapse rates than subjects in the medication group [112]. The benefits of ten weeks of supervised weight-lifting followed by 10 weeks of unsupervised training were maintained at 26 months in a controlled trial [113]. DiLorenzo et al. also reported positive results in a one-year follow-up [114], but their sample was non-clinical and there was no control group.

6. AIMS OF THE STUDY

The general aim of the study was to compare the effect of two interventions on mood: 1) aerobic physical exercise and 2) bright light exposure, either alone or combined, in healthy, working-age volunteers with varying numbers of depressive symptoms. Possible interactions between these two interventions in relation to mood have not been studied previously. We hypothesized that light and exercise together would have cumulative positive effects on mood. The second primary aim was to investigate possible behavioural factors that could be used to predict either a good response or early drop-out by an individual. The specific aims of each of the four published reports were as follows:

I To establish the efficacy of exercise, with or without bright light exposure, in treating depressive symptoms. The study groups were 1) exercise sessions with bright light exposure, 2) exercise sessions in normal gym illumination, and 3) stretching-relaxation sessions in a dimly-lit environment. The "efficacy-study".

II To investigate whether adding bright light exposure to physical exercise improves the outcome of mood compared to physical exercise alone. The "add-on study".

III To compare the effect of bright light exposure with or without exercise on mood with exercise alone. The "bright-light study".

IV To identify possible behavioural factors predicting *either* beneficial effects of light, exercise, *or* their combination, or early drop-out from the study. The "prediction study".

7. SUBJECTS AND METHODS

7.1 Settings

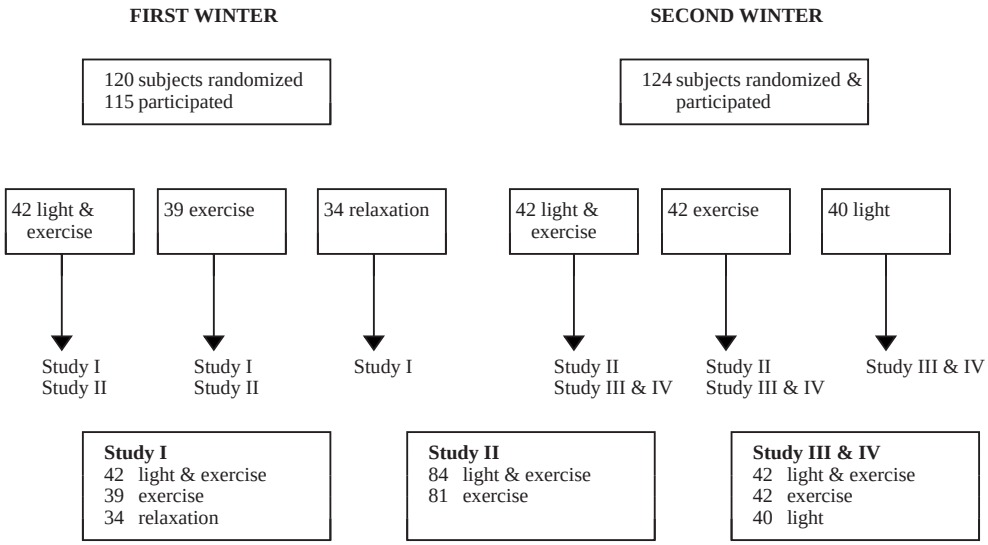
The trial was carried out at the Vita Health Services' gym (Mikonkatu, Helsinki). The gym was normally lit with regular lamps (F36W/186) emitting cool-white fluorescent light (6000 K). For administration of additional bright light, 30 extra light fixtures with cool-white (6000 K) fluorescent lamps (F58W/186, Sylvania, Germany) were attached to the ceiling of the gym. The bright light lamps could be turned on and off independently of the regular lighting of the gym. The intensity of light was repeatedly checked to be at least 2500 lux at eye-level when the extra light fixtures were on.

7.2 Subjects

The subjects were enrolled through occupational health care centres, which delivered a recruiting letter to all employees of their customers, yielding a target population of approximately 15,000. The letter invited subjects who felt they routinely experienced difficulties during the dark winter months, and were interested in a study of physical exercise, to contact the staff of their centre. The study protocol was explained to the volunteers in a face-to-face meeting with a health professional. The eligibility of subjects was checked by the chief physician of each centre, who was blind to the randomization procedure. Block randomization was done by the staff of each occupational health centre according to lists provided by the investigators. The physiotherapists who supervised the groups were not involved in the randomisation, and were blinded to study code before treatment allocation.

To be included in the study, the subject had to be at least 18 years old. Exclusion criteria were progressive retinal disorders which could have been exacerbated by exposure to bright light, severe general medical conditions preventing physical exercise, and major psychiatric disorders requiring specialist attention or regular psychotropic medication. Figure 1 shows the allocation of study subjects .

Figure 1. Allocation of study subjects.



7.3 Study protocol

Because of spatial and temporal limitations the trial had to be conducted in two distinct parts during two consecutive winters, and the number of study groups per trial had to be limited to three. In both winters, the study lasted from the end of November to the end January, eight weeks in total.

The two constant groups were exercise in bright light and exercise in the normal gym illumination. During the first winter the exercise consisted of aerobic fitness training tailored by a physiotherapist individually for each subject, using the gym equipment two or three times a week in the morning or early afternoon. During the second winter there were group aerobics training sessions led by a physiotherapist twice a week. The group sessions started at 7:30 am or 8:30 am from Monday to Friday and at 10:00 am or 11:00 am on Saturdays. The exercise sessions lasted approximately an hour, of which 15 minutes was reserved for stretching and warm-up to avoid injuries. The physiotherapists regularly controlled the subjects' attendance and the intensity of the training in both winters.

In the first winter, the third group participated in relaxation / stretching sessions for 45 minutes once a week in a dimly lit room. These sessions were intended to be a placebo condition both in relation to bright light exposure, and physical exercise. In the second winter, the third group participated in relaxation / stretching sessions in bright light, in the same gym where the aerobics sessions were held, lasting for 45 minutes twice a week. The relaxation / stretching sessions were designed specifically to avoid raising the heart beat, and were assumed to be a placebo condition in relation to physical exercise.

7.4 Ethics

All subjects were at least 18 years of age at enrolment and signed an informed consent form prior to participation in the study. The ethics committee of the National Public Health Institution approved the study protocol.

7.5 Assessment

The subjects filled in the Seasonal Pattern Assessment Questionnaire (SPAQ; [33]) and the Structured Interview Guide for the Hamilton Depression Rating Scale - Seasonal Affective Disorders Version Self-Rating Format (SIGH-SAD-SR; [115]) at the baseline At 4 and 8 weeks and at follow-up 4 months after the study, the participants were asked to fill in the SIGH-SAD-SR. The SPAQ measures seasonal mood and behavioural changes, and the total of its 6-item scale gives the Global Seasonality Score (GSS). The SIGH-SAD-SR includes the Hamilton Depression Rating Scale (HDRS), plus an 8-item addendum for measuring the atypical depression symptoms (ATYP).

The baseline assessment was augmented for the second winter. Before the study start, the subjects filled in the Basic Nordic Sleep Questionnaire (BNSQ)[116], and a modified 26-item questionnaire from the population risk factor survey in Finland (FINRISK) [117] in addition to the questionnaires previously mentioned. The BNSQ has 21 questions measuring the quality and length of sleep and problems related to sleep. The abbreviated FINRISK consists of 26 questions concerning smoking, alcohol consumption, dietary fat intake, cholesterol, and habitual exercise.

At the start, and at weeks 4 and 8, all subjects were weighed to assess body mass index (BMI). The subjects in the exercise groups participated in a fitness test immediately before and after the study period. In the first winter, this included 5 items primarily measuring the endurance and flexibility of back muscles. In the second winter, subjects in the exercise groups participated in a two-kilometre walking test which predicts the maximal oxygen uptake using a model with age, sex, walking time, BMI, and heart rate at the end of the test as variables [118].

7.6 Statistics

Statistics were calculated using the SPSS for Windows (Versions 8.0 to 13.0, SPSS Inc.) and the S-PLUS 2000 Professional Edition for Windows (Mathsoft Inc.).

Outcome measures were the absolute scores of the HDRS and the ATYP as well as the changes in these scores from baseline to week 8. A 50% decrease on the HDRS or ATYP was used as a criterion for treatment response. General linear models were employed, and one-way analysis of variance (ANOVA) and independent samples t-test were performed where applicable. The data was evaluated by examining the mean and 95% confidence interval (CI) of each outcome measure. A linear mixed-effects model was constructed to estimate the effect of light and exercise as separate factors [119, 120].The baseline score for the relevant outcome variable, sex, age, and the GSS were entered in the models as co-variates. Logistic regression models were used to assess the effect of baseline characteristics, with the defined outcome as the dependent variable.

8. RESULTS

8.1 Study I – "Efficacy"

Study groups:	I	Bright light & exercise
	II	Exercise in normal illumination
	III	Stretching / relaxation in dim illumination

Complete data were received from 81 subjects, 9 males and 72 females, with a mean age of 40.9 years (range 22 to 67). Of these subjects, 30 were assigned to group I, 30 to group II, and 21 to group III.

8.1.1 Hamilton Depression Score

The mean (S.D.) HDRS at the baseline was 12.6(5.9), 10.9(6.8), and 9.8(5.3) in groups I, II, and III respectively ($F=1.84$, $p=.17$). During the eight-week study period, the relative mean decrease in HDRS from the baseline value was 66% in group I, 45% in group II, and 12% in group III. The difference in the absolute change between study groups was highly significant ($df=2$, $F=11.6$, $p<.001$). *Post Hoc*-tests (Bonferroni) indicated that mean differences were significant between groups I and II ($p=.046$), groups I and III ($p<.001$), and groups II and III ($p=.039$). The results did not change when age, sex, and GSS were added to the equation as co-variates. Baseline HDRS was a highly significant factor, indicating that subjects with highest baseline HDRS benefited most.

8.1.2 Atypical Symptom Score

The mean ATYP (S.D.) at the baseline was 8.82(5.7) in group I, 5.14(4.2) in group II, and 6.32(4.1) in group III ($F=5.64$, $p=.005$). The relative decrease in the ATYP was highest in group I, 85%. In groups II and III the relative decrease was 32% and 24% respectively. In *Post Hoc* tests (Bonferroni) both the difference between groups I and II and between groups I and III was highly significant (for both, $p=.001$). When the GSS, age, and sex were included in the general linear model as co-variates, these results did not change, and were found to be non-significant. Baseline ATYP was a highly significant co-variate.

8.2 Study II – "Add-on"

Study groups:	I	Bright light and exercise
	II	Exercise

Complete data were received from 121 subjects, 14 males and 107 females, with a mean age of 41.8 years (range 22 to 63). Of these subjects, 62 were assigned to group I, and 59 to group II.

8.2.1 Hamilton Depression Score

The baseline Hamilton score was higher in group I than group II, 12.2(7.1) vs. 9.89(6.0), F=4.7, p=.03. The average relative change in HDRS during the study was -53% in group I and -36% in group II, the absolute change being significantly higher in group I than group II (F=7.47, p=.007). In general linear models, the GSS, age, and sex were not significant co-variates, whereas baseline HDRS was highly significant. Whether the subject had participated in the "Efficacy study" or the "Bright light study", was not a significant co-variate.

8.2.2 Atypical Symptom Score

Baseline ATYP was higher in group I than in group II (7.62(5.4) and 5.21(4.0), F=9.35, p=.003). The ATYP in both groups, was significantly reduced during the study period. In group I, the mean relative change was 68%, and 28% in group II. There was a highly significant difference between the groups (F=20.3, p<.001).Group remained a significant factor (F=8.18, p=.005) In the general linear models. Baseline ATYP was a significant co-variate, but age, sex and the GSS were not.

8.3 Study III – "Bright-light"

Study groups:	I	Bright light and exercise
	II	Exercise in normal illumination
	III	Stretching / relaxation in bright light

Complete data were received from 98 subjects, 11 males and 87 females, with a mean age of 43.4 years (range 26 to 63). Of these subjects, 32 were assigned to group I, 29 to group II, and 37 to group III.

8.3.1 Hamilton Depression Score

Baseline HDRS was 11.9(8.1), 8.9(5.0), and 12.1(6.6) in groups I, II, and III, respectively (df=2, F=2.66, p=.07), the relative change in the HDRS during the study being -40%, -23%, and -33% respectively. The absolute change in the HDRS between study groups was not significant (df=2, F=1.56, p=.22). All interventions effectively reduced the HDRS: Light&Exercise (t=3.83, df=31, p=.001), Exercise (t=2.71, df=28, p=.011), and Light (t=3.84, df=36, p<.001).

In the repeated-measures analysis with light and exercise as factors, exercise reduced the HDRS significantly (-2.5, 95% CI -4.6 to -.4, p=.02), and there was a trend towards bright light also reducing the HDRS (-2.5, 95% CI -4.4 to 0.0, p=.05). However, the difference between the effects of the two interventions was not significant (Wald test, χ^2=.08, p=.8).

8.3.2 Atypical Symptom Score

Baseline ATYP was 6.48(4.9), 5.28(3.9), and 6.67(4.5) in groups I, II, and III, respectively (df=2, F=1.06, p=.35), relative change in the ATYP during the study being -45%, -22%, and -40% respectively. The absolute change in the ATYP between study groups was not significant (df=2, F=1.64, p=.20). However, with-in group comparison showed that the ATYP was effectively reduced only in the intervention groups with exposure to bright light: group I (t=4.0, df=31, p<.001), and group III (t=3.72, df=36, p=.001). In the Exercise group (group II), the reduction in the ATYP was not statistically significant.

In the repeated-measures model with bright light and exercise as factors, light reduced the ATYP significantly (-2.0, 95% CI -3.6 to -.3, p=.02), whereas exercise did not (-.4, 95% CI -2.0 to 1.1). The difference between the effects of the two interventions was significant (Wald test, χ^2=4.5, p=.03).

8.4 Study IV – "Prediction"

Study groups:	I	Bright light and exercise
	II	Exercise in normal illumination
	III	Stretching / relaxation in bright light

Since the study group was the same as in study III, complete data was received from 98 subjects (11 men, 87 women) with a mean (S.D.) age of 43.4 (9.5), ranging from 26 to 63 years. Sixty-nine subjects were assigned to the light therapy groups, and 61 subjects to the aerobic exercise treatment groups. Thirty-two of these subjects were in the combined intervention group.

8.4.1 Treatment response

Based on the HDRS, 42 subjects (5 men, 37 women, χ^2=.9) were classified as responders. Thirty-five (83%) had had light therapy, 24 (57%) had been in the aerobic exercise groups, and 17 subjects (40%) in the combined group. Overall, light had a significant effect on the number of responders, as assessed with the HDRS (χ^2=.02). The number needed to treat (NNT) for light was 3.8.

Based on the ATYP, 51 subjects (8 men, 43 women) were classified as responders. Thirty-seven (73%) had been in the bright light groups, 30 (59%) in the exercise groups, and 16 (31%) had been in the combined exercise and light group.

Logistic regression models were formulated, with response on the HDRS or the ATYP as the dependent variable. These yielded few results. On the HDRS, a worse outcome was predicted by self-reported previous high cholesterol (p=.01) and higher alcohol consumption (>7 drinks per week, p=.008). A worse outcome on the ATYP was independently predicted by higher alcohol consumption (p=.04), and self-reported low quality of sleep (p=.002). A better response on the ATYP was predicted by self-reported initial insomnia, trouble falling asleep (p=.01).

8.4.2 Dropout from the study

There were 26 subjects (21%) classified as dropouts (4 male, 22 female, χ^2=.6), 8 (20%) in group I, 13 (31%) in group II, and 5 (12%) in group III (χ^2=.1). Dropout-status was significantly influenced by having a higher GSS (F=5.40, p=.02) and having attended less treatment sessions (F=143.0, p<.001). There was a trend towards baseline HDRS having an effect on dropout-status (F=4.00, p=.05). Worse pre-intervention fitness (in the exercise groups) was predictive of dropout status (F=11.1, p=.001), and there was also a significant Treatment group $*$ Dropout interaction (F=7.82, p=.007). Initial insomnia, derived from the BNSQ, was also a significant factor (F=6.00, p=.02, Treatment group $*$ Dropout interaction F=5.43, p=.006).

8.5 Summary of the results

The main finding of the study was that both exercise and bright-light exposure were effective in treating depressive symptoms. When the interventions were combined, the relative reduction in the HDRS was 40 to 66%, and 45 to 85% in the ATYP during the eight-week trial. Bright light exposure was more effective than exercise in treating atypical depressive symptoms. However, the seasonality trait, as measured on the SPAQ, was not found to be of predictive value. Even subjects with low seasonality score benefited from these interventions. No single factor could be found that would predict a good response to treatment intervention with bright light and/or physical exercise. Drop-out from exercise groups was predicted by lower pre-intervention fitness test results.

9. DISCUSSION

9.1 Exercise

Physical exercise seems to be a promising treatment option for major depressive disorder, population studies showing a positive correlation between physical activity and mood. The immediate effects of a single bout of exercise have been studied quite extensively [121], and 20-30 minutes of moderate intensity exercise seems to have positive mood effects both on depressed and non-depressed subjects. Less is known about the long-term effect of exercise on "normal mood", or on the mood of subjects with depressive symptoms.

A much-quoted study by Lennox et al. (1990) evaluated the effect of thirteen weeks of aerobic exercise on the mood of non-depressed subjects [122]. Comparison groups were non-aerobic exercise and waiting-list controls. Significant improvements in physical fitness were apparent, but no change in mood was observed. The authors conclude that exercise does not appear to have any long-term beneficial effect on the mood of non-depressed individuals selected from a normal, i.e., non-clinical, population. In a study of sedentary, mildly hypertensive volunteers [123], brisk walking for 40 minutes three times a week for six months was not associated with mood improvement compared to the control group.

However, most of the more recent research seems to contradict these findings. Ten weeks of moderate cardiovascular exercise (20 to 30 minutes, 3 times a week) decreased the Profile of Mood States (POMS) depression score significantly, and the difference from a no-exercise control group was also significant [124]. Neither change in cardiovascular fitness or the baseline POMS depression score were correlated with the changes in the depression score. In a study by DiLorenzo et al. (1999), a twelve-week aerobic exercise program significantly improved the mood [114] of the participants, and the benefit was maintained at twelve-month follow-up. The authors postulate that the mood changes were caused by improvement in fitness, but do not present any direct evidence for this.

The results of the present study are in agreement with most of the previous research. Our results show that subjects with "normal" or "near-normal" mood could benefit from an exercise treatment program. The benefit increased the more depressive symptoms a person had. The "flooring-effect" starts to work when the baseline depressive symptom score gets lower. Pre-exercise depressive mood predicts mood improvement even after a single aerobic exercise session [125].

Exercise intensity was not measured in this study. Changes in fitness test results were not correlated with mood improvements. Other studies of the effect of exercise on mood have reported either correlation between mood and cardiovascular improvements [114] or no correlation [124]. The main finding of this study was that physical exercise and bright light exposure seem to alleviate depressive symptoms during wintertime, even when administered at a "low dose", twice a week. Recent research suggests that to treat clinical depression effectively, exercise intensity should be at least moderate, corresponding to public health recommendations, and five times a week brought better results than exercising three times a week [110]. Most studies reporting positive mood effects have used exercise programs of 2-3 treatment sessions per week [18, 111]. The findings of Dunn et al. (2005) cannot be directly compared to the present study, as their study subjects were MDD patients. Even very light exercise programs (3 times a week, 20 to 30 minutes per session) have shown positive effects in subjects with depressive symptoms [124].

A Swiss study by Suter et al. (1991) also found that regular jogging was associated with improvements in mood [126]. However, they also noted that these changes in mood were superimposed by seasonal changes in mood (the deterioration of mental well-being during the winter months and remission in summer), and claim that regular jogging of approximately 10 to 15 km/week may help to diminish the deterioration of mood observed during the winter months. However, these results have not been replicated.

An interesting finding is that those who completed the study (Study III-IV) were in better physical condition in the pre-intervention fitness test than those who dropped out. Regular exercise may be a representation of self-motivation trait, which would increase adherence to a therapeutic exercise program [127]. Exercise habits are closely related to self-perception and perceived self-importance [128]. A common problem with exercise programs is adherence, motivational factors being especially prevalent with depressed patients. We did not have recruitment problems (except the overwhelming gender ratio), probably because our subjects were not from a clinical population.

A higher drop-out rate with subjects, who initially were not as fit, also suggests that exercise treatment programs should be tailored for individuals more closely than before. The worst scenario is a sedentary person who drops out early just because the exercise program feels too strenuous. Slow, progressive treatment programs have been used in the treatment of chronic fatigue syndrome [129].

9.2 Bright light

Atypical depressive symptoms are the best predictors of treatment response in trials of BLT, and atypical symptoms are more commonly present in SAD than non-seasonal depression. We found that BLT, administered twice a week, either combined with exercise or not, reduced the atypical symptom scores during the eight-week study period, whereas exercise without BL exposure did not have this effect on atypical symptoms. The clinical implication seems to be clear, even though the difference between treatment groups failed to reach statistical significance. BL administered only twice a week, and possibly combined with physical exercise, effectively reduces the atypical depressive symptoms often associated with 'winter blues'.

A novel finding in the study was that BL exposure even without exercise and administered twice a week equalled the exercise program in efficacy, with or without BL (Study III). According to previous research on BLT, twice-a-week light therapy could and should be labelled as a placebo condition. However, the treatment recommendations have been formulated based on studies of bright light treatment of SAD. The findings of the study seem to suggest that light exposure only twice a week could be effective in alleviating depressive symptoms. However, these results need to be confirmed in future research.

9.3 Bright light & exercise

This seems to be the first study which considers the mood effects of combined physical exercise and bright light exposure in a randomized, controlled setting. One finding was that atypical depressive symptoms seemed to respond to bright light more effectively than to exercise. Similar results have been reported from Siberia [130]. The authors report that winter depression responded equally well to exercising and light, while a significant therapeutic difference in favour of exercising was found in non-seasonal depression. Groom & O'Connor from the University of Tulsa (1996) present the interesting hypothesis that those exercisers whose habits exposed them to a relatively large amount of light reported fewer seasonal depressive symptoms than those whose habits exposed them to a relatively small amount of light [131]. They propose that light exposure should be considered as a possible confounding variable in studies of exercise and mood. Our results suggests that at least subjects with atypical depressive symptoms may benefit more from light exposure than exercise.

9.4 Drop-out from the study

The dropout rate was relatively low, approximately 20% for all studies combined, and did not differ significantly between the intervention groups. There seemed to be a trend towards subjects in groups receiving bright light therapy adhering to the study more closely than subjects in the exercise groups and relaxation in dim light-group. Subjects might have felt bright light therapy was a novel, more attractive treatment option than plain, 'old-fashioned' exercise. We tried to minimize this problem by emphasising 'exercise trial' in leaflets provided for possible volunteers. It was not possible to avoid this problem altogether, and probably a placebo effect of at least some degree is present in the BL groups. This is a problem in all BLT studies, as mentioned earlier. One solution would be to measure pre-intervention expectations before randomization, but this had to be omitted from our study for practical reasons. However, the dropout rates did not differ between the groups, and these numbers are similar to the rates reported previously by other groups [132].

9.5 Limitations of the study

A self-rating version of the Hamilton Depression Rating Scale was used. A rating scale originally designed for the follow-up of severely depressed in-patients might be argued not to be a proper instrument for subjects with normal or near-normal mood. The HDRS correlated strongly with subjective change in mood [133], and the HDRS from the SIGH-SAD-SR gave similar scores with the observer-rated HDRS [134].

There was a sizable preponderance of women in our study. This is probably not a confounding factor, since menstrual-cycle stage and menopausal state do not seem to have a marked effect on symptom reporting [135]. However, this limits the generalizability of the results to the general population.

9.6 Implications and future research

This study shows for the first time that depressive symptoms during winter can be treated with an exercise program, with or without BL. However, we did not address the possible mechanisms. In both depression and SAD, the circadian rhythms are often disturbed. Both exercise and BL seem to fix these disturbances in the circadian rhythms, but this does not fully explain their mood-lifting effects. Other possible mechanisms could be hormonal or psychological. Exercise and BL increase serotonergic neural transmission, as well as acting on the neurotrophic factors, which may be essential in the pathophysiology of depression.

Studies on the effect of bright light and exercise on mood should perhaps be replicated in clinical populations, and biological markers should be explored, as this could eventually lead to the origin of affective disorders in humans.

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